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File: ■ Cocoa (*Theobroma cacao*, Malvaceae)
■ Cardiovascular Health

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RE: Cocoa Flavanol Consumption Improves Vascular Function in Healthy Subjects

Sansone R, Rodriguez-Mateos A, Heuel J, et al.; for the Flaviola Consortium, European Union 7th Framework Program. Cocoa flavanol intake improves endothelial function and Framingham Risk Score in healthy men and women: a randomised, controlled, double-masked trial: the Flaviola Health Study. *Br J Nutr*. 2015;114(8):1246-1255.

Flavanol intake has been associated with improvement in arterial function in persons with cardiovascular disease (CVD) and in those at risk for developing the disease. Published studies have specifically linked flavanol consumption with recovery of endothelial function, decreased blood pressure (BP), and improved lipids and insulin resistance, most often in individuals at increased cardiovascular risk. Whether the intake of cocoa (*Theobroma cacao*, Malvaceae) flavanols (CFs) can maintain or improve cardiovascular health in healthy individuals has not been evaluated. These authors conducted the Flaviola Health Study, a randomized, controlled, double-masked trial, to investigate the effects of dietary CF intake on markers of cardiovascular risk in healthy, middle-aged individuals without any history, signs, or symptoms of CVD.

The primary endpoint of endothelial function was measured by flow-mediated dilation (FMD); secondary endpoint assessments included plasma lipids, BP, and markers of arterial stiffness – pulse wave velocity (PWV) and augmentation index (AIX). Using the Framingham Risk Prediction model, the authors calculated the 10-year risk for each subject to develop coronary heart disease (CHD) or CVD, to experience a myocardial infarction or stroke, or to die from CHD or CVD.

The study was conducted at the Division of Cardiology, Pulmonology and Vascular Medicine at Duesseldorf University in Duesseldorf, Germany, from February 2013 to August 2014. Subjects were recruited through word of mouth and postings at the university and its outpatient clinic. The authors selected 105 middle-aged (35-60 years) healthy Caucasian men and women without any history, signs, or symptoms of CVD and with a body mass index of 23-27 kg/m^2.

An open-label pilot study in 5 male subjects preceded the trial. Those 5 subjects received 450 mg of CFs twice daily for 1 month to verify the efficacy of the flavanol drink

in increasing FMD and to assess the effect size and timing of the main study. FMD was measured in fasting subjects and at 1 and 2 hours after consumption of the first drink on days 1, 7, 14, 21, and 28. The authors discovered that CF intake led to a time-dependent increase in endothelial function that plateaued after 2 weeks.

The remaining 100 subjects, assigned to 1 of 2 parallel groups of 50 subjects each, then participated in the 1-month, double-masked, randomized, controlled trial. Two interventions were provided as a low-energy, fruit-flavored beverage mix (provided by Mars, Inc.; McLean, Virginia), which was combined with 50 mL water and consumed twice daily, at breakfast and with the evening meal. A high-flavanol Cocoapro®-processed cocoa extract (Mars, Inc.) was added to provide 450 mg total CFs per serving in the flavanol group drink, with (–)-epicatechin being the predominant monomeric flavanol. The Cocoapro process used to extract CFs from the beans helps to preserve and protect the flavanols usually destroyed during normal cocoa processing, according to Mars, Inc. The control beverage contained no cocoa extract; however, because of the natural presence of theobromine and caffeine in the cocoa extract, both were added to the control beverage to match the composition of the flavanol drink.

All measurements were taken in fasting subjects at baseline and at 2 hours after the first drink on day 1 and again at those time points after consuming the last drink at the end of the trial. Subjects were asked to avoid excess amounts of flavanol-rich foods for 24 hours before study visits. No significant baseline differences were seen in demographic parameters between the 2 groups. Flavanol intake was low among all subjects, and the subjects exhibited a low risk for developing or dying from CVD.

The results of this trial demonstrated that flavanol consumption increased FMD significantly over the control drink by a difference of 1.2% after 1 month. In a published meta-analysis, a 1% improvement in FMD was associated with an 8% decrease in overall CVD risk over 3 to 6 years.[1]

Flavanol consumption for 1 month also significantly decreased office systolic BP (difference of 4.4 mm Hg) and diastolic BP (difference of 3.9 mm Hg) compared with consumption of the control drink. Significant lowering was seen in central systolic BP (by 4.3 mm Hg) and diastolic BP (by 4.7 mm Hg) responses in the flavanol group compared with the control group. After 1 month, PWV and AIX decreased by 0.4 m/s and by 5.3%, respectively, more in the flavanol group than in the control group. The authors point out that no other study of this scale has examined whether flavanols can decrease BP in healthy subjects with normal BP. These findings suggest that improved elasticity of arteries or arterial unloading, as evidenced by the decreases in PWV and AIX, may be related to systolic BP lowering. Future studies of longer duration should verify the biological relevance of these findings and examine the mechanisms involved, say the authors.

Significant differences in decreases were seen in total cholesterol (0.20 mmol/L or 7.7 mg/dL) and low-density lipoprotein cholesterol (0.17 mmol/L or 6.6 mg/dL), with greater decreases observed in the flavanol group. High-density lipoprotein cholesterol increased by 0.10 mmol/L, or 3.9 mg/dL, more at 1 month after flavanol intake compared with control.

At baseline on day 1, fasting levels of total plasma flavanols were not detectable in 98 subjects. After 2 hours, acute ingestion of CFs led to a significant increase in plasma

flavanols and metabolites, with values similar to those observed after acute ingestion on day 1 of the study. After 1 month of CF consumption and following an overnight fast, the levels were again below the limit of detection in all but 7 subjects.

The authors reported significant correlations between the increase in FMD and the increase in plasma flavanols 2 hours after consumption ($P<0.0001$) and between chronic FMD improvements at 1 month and the acute increase in plasma flavanols at 2 hours after consumption as an index of individual flavanol bioavailability ($P<0.0001$).

Compared with the control group, flavanol consumption led to significant decreases in CVD risks as measured by Framingham Risk Scores. The decreases in the flavanol group compared with baseline were as follows: to be diagnosed with CHD (21%) or CVD (22%); to experience myocardial infarction (31%); and to die from CHD (37%) or CVD (30%).

In this study, CF consumption improved the parameters of vascular function in healthy, middle-aged subjects. "Our findings support the notion that CF intake has the potential to support the maintenance of cardiovascular health," write the authors.

This study was partially funded by Mars, Inc. One of the authors (H. Schroeter) reported a conflict of interest, as he is employed by Mars, Inc., a company engaged in flavanol research and flavanol-related commercial activities and a member of the Flaviola Research Consortium.

—*Shari Henson*

Reference

[1]Ras RT, Streppel MT, Draijer R, Zock PL. Flow-mediated dilation and cardiovascular risk prediction: a systematic review with meta-analysis. *Int J Cardiol*. 2013;168(1):344-351.

Referenced article can be accessed at http://journals.cambridge.org/action/displayAbstract?fromPage=online&aid=9987939&fileId=S0007114515002822.

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